Bevacizumab for recurrent ependymoma

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ABSTRACT

Background: Ependymoma is a rare type of glioma, representing 5% of all CNS malignancies. Radiotherapy (RT) is commonly administered, but there is no standard chemotherapy. At recurrence, ependymoma is notoriously refractory to therapy and the prognosis is poor. In recurrent glioblastoma, encouraging responses with bevacizumab have been observed.

Methods: In this Institutional Review Board–approved study, we retrospectively analyzed the records of 8 adult patients treated for recurrent ependymoma and anaplastic ependymoma with bevacizumab containing chemotherapy regimens. We determined radiographic response (Macdonald criteria), median time to progression (TTP), and median overall survival (OS; Kaplan-Meier method).

Results: There were 4 men and 4 women with a median age of 40 years (range, 20–65). Prior treatment included surgery (n = 8), RT (8), temozolomide (5), and carboplatin (4). Bevacizumab (5–15 mg/kg every 2–3 weeks) was administered alone (2) or concurrently with cytotoxic chemotherapy including irinotecan (3), carboplatin (2), or temozolomide (1). Six patients achieved a partial response (75%) and 1 remained stable for over 8 months. Median TTP was 6.4 months (95% confidence interval 1.4–7.4) and median OS was 9.4 months (95% confidence interval 7.0–not reached), with a median follow-up of 5.2 months among 5 surviving patients (63%).

Conclusions: The radiographic response rate to bevacizumab-containing regimens is high. A prospective study is warranted. ***Neurology*® 2009;73:1677–1680**

GLOSSARY

CI = confidence interval; **OS** = overall survival; **RT** = radiotherapy; **TTP** = time to progression; **VEGF** = vascular endothelial growth factor.

Ependymomas are CNS neuroepithelial tumors that are thought to arise from ependymal cells in supratentorial, infratentorial, and spinal locations. They are rare, comprising approximately 5% of all CNS malignancies.[1] Ependymoma (WHO grade II) and anaplastic ependymoma (WHO grade III) are characterized by local recurrence and distant metastasis through CSF pathways despite maximal resection and regional radiation therapy (RT). In contrast to other glioma subtypes such as glioblastoma, the low incidence limits the capability to conduct large prospective clinical trials, and management is based mainly on small case studies. Retrospective series in recurrent disease suggest that approximately one-third of patients respond to platinum-based chemotherapy regimens, and nitrosoureas also may benefit individual patients,[2] but most patients have stable disease as best response and true regression is uncommon. Consequently, there is no standard chemotherapy regimen.

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), preventing the binding of VEGF to its receptors on the surface of endothelial cells. Bevacizumab is active

Supplemental data at www.neurology.org

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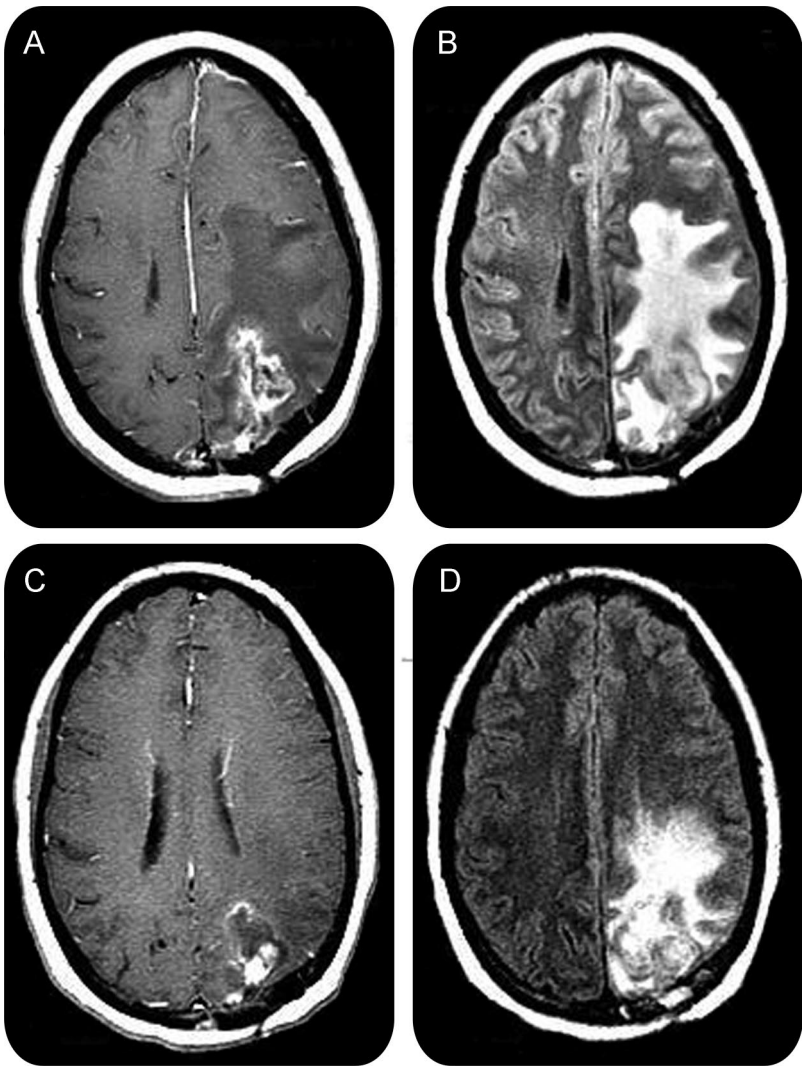
against colorectal, non-small cell lung, and breast cancers, and has demonstrated promising activity in other malignant gliomas, such as glioblastoma, for which it received accelerated approval from the Food and Drug Administration.[3,4] In addition, ependymomas express VEGF.[5] Therefore, we report our experience treating 8 patients with recurrent ependymoma or anaplastic ependymoma using bevacizumab alone or in combination with chemotherapy.

METHODS We retrospectively identified adults treated for recurrent ependymoma or anaplastic ependymoma with bevacizumab-containing chemotherapy regimens since 2006 (when bevacizumab became widely used for gliomas). We sought to determine radiographic response (Macdonald criteria)[6] and estimated median time to progression (TTP) and overall survival (OS) by the Kaplan-Meier method (level of evidence class III, level U) from the beginning of bevacizumab. Data were updated as of April 16, 2009.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Memorial Sloan-Kettering Cancer Center; the University of California, Los Angeles; and the University of Lausanne Institutional Review Boards with a waiver of consent.

RESULTS There were 8 patients, 4 of whom were women, with a median age of 40 years (range, 20–65). Five patients had supratentorial disease, 2 infratentorial disease, and 1 both. Prior treatment included surgery and RT in all, temozolomide in 5, and carboplatin in 4. Bevacizumab (5–15 mg/kg every 2–3 weeks) was administered as monotherapy to 2 patients and combined with cytotoxic agents in 6: irinotecan (3), carboplatin (2), or temozolomide (1). All patients were evaluated for best radiographic response, which was partial in 6 (figure), stable (for >8 months) in 1, and progressive disease in 1 (table), giving a 75% radiographic response rate. Among 4 patients with carboplatin-resistant disease, 3 responded (table). Median TTP was 6.4 months (95% confidence interval [CI] 1.4–7.4) and median OS was 9.4 months (95% CI 7.0–not reached). Median follow-up was 5.2 months among 5 surviving patients (63%). Clinical improvement was also observed in 2 of the 6 patients who were both symptomatic and achieved either radiographic response or stabilization. In the single patient taking corticosteroids, bevacizumab treatment enabled discontinuation.

Figure **Partial radiographic response**



The contrast enhancing (A) and fluid-attenuated inversion recovery (B) abnormality on the baseline imaging substantially improved during treatment in a patient treated for supratentorial disease (C, D).

DISCUSSION Ependymoma is a rare CNS tumor for which there is no standard chemotherapy and few published reports of active agents. A retrospective study of various chemotherapy regimens in 28 adults with recurrent cerebral ependymoma (17 WHO grade II; 11 WHO grade III) identified an overall response rate of 21%, median TTP of 9.9 months (95% CI, 7.5–21.7), and median OS of 40.7 months (95% CI, 16–not reached).[2] Platinum-containing regimens appeared to be the most beneficial, but only a minority of patients (31%) responded.[2] A phase II study of temozolomide, the most commonly prescribed chemotherapy for other glioma subtypes,[7] yielded no responses among 14 children and adolescents with recurrent ependymoma.[8] A preliminary report of a prospective study suggests some adults benefit from temozolomide.[9]

Immunohistochemical and in situ hybridization studies show significant VEGF expression by ependymomas.[5] Serial measurement of serum VEGF in pediatric patients treated with RT for ependymoma showed a significant decline in the 12 months

Table Patient characteristics and outcome

Patient	Gender	Histology	Prior therapy	Age at start of bevacizumab, y	Tumor location at start of bevacizumab	Leptomeningeal disease	Concurrent therapy with bevacizumab	Best response to bevacizumab containing regimen	Time to progression after starting bevacizumab, mo	Overall survival after starting bevacizumab, mo
1	F	AE	RT	20	S	No	TMZ	PR	7.4	35.6+
2	M	E	RT	52	S	No	Carbo	PR	6.4	7.8
3	F	E	RT, TMZ	29	S	No	Carbo	Stable disease	8.1+	8.6+
4	M	AE	RT, TMZ, Carbo	65	S	Yes	Irinotecan	PR	3.7	7.0
5	M	AE	RT, TMZ	23	I	No	Irinotecan	PR	6.5	9.4
6	M	E	RT, Carbo, tamoxifen	63	I	Yes	None	PR	3.2+	3.7+
7	F	AE	Carbo, etoposide, ifosfamide, SCT, RT, TMZ, MTX, cytarabine	29	S, I	Yes	Irinotecan	PR	4.0	22.8+
8	F	AE	RT, Carbo, etoposide, TMZ	50	S	Yes	None	Progressive disease	1.4	2.1+

AE = WHO grade III anaplastic ependymoma; RT = radiotherapy; TMZ = temozolomide; PR = partial response; + = censored for progression and/or survival; E = WHO grade II ependymoma; Carbo = carboplatin; I = infratentorial; MTX = methotrexate; S = supratentorial; STC = stem cell transplant.

following treatment.[10] Therefore, VEGF inhibition may be an effective strategy in the treatment of ependymoma. We observed responses in 6 of 8 patients and clinical benefit (response or stabilization) in 7 treated with bevacizumab-containing regimens.

Moreover, our patients represent a subgroup with a particularly poor prognosis. All had recurrent disease after surgical resection and radiation therapy, and 6 had also received chemotherapy for prior recurrences, including a platin in 4. Nevertheless, we found that 75% responded to bevacizumab-containing regimens, and 88% achieved at least temporary disease control.

Radiographic assessment of glioma response to antiangiogenic therapy is problematic. Traditional criteria depend upon serial measurement of the cross-sectional area or volume of contrast-enhancing tumor.[6] Like corticosteroids, VEGF inhibitors such as bevacizumab decrease vascular permeability, reducing both cerebral edema and contrast enhancement. Therefore, it is possible that the apparent responses we observed reflect restoration of a disrupted blood–brain barrier. However, leptomeningeal disease, in which there is no tumor mass disrupting the blood–brain barrier, also responded to bevacizumab (figure e-1 on the *Neurology*® Web site at www.neurology.org). In addition, the 95% CIs for our median TTP and OS overlap with those reported by others for platinum-based therapy (5.2 months–not reached for TTP and 21 months–not reached for OS),[2] suggesting that bevacizumab-containing regimens are not inferior. Furthermore, we observed responses or stabilization in 75% (3 of 4) of platinum-resistant tumors and 80% (4 of 5) of temozolomide-resistant tumors. Finally, radiographic response or stabilization was associated with clinical improvement or reduced corticosteroid dependence in 3 patients.

Six of our patients (table) with stable disease or partial response received concurrent carboplatin, temozolomide, or irinotecan, making it difficult to attribute disease stability control to bevacizumab alone. In addition, prior therapy in all of our patients was heterogeneous; therefore, we cannot exclude the possibility that patients treated earlier in the course of their disease might have a tumor that is more sensitive to therapy in general. Nonetheless, in some patients, use of bevacizumab-containing regimens appears to delay tumor progression and may be reasonable depending on potential cost and risk tolerance. The true efficacy of bevacizumab in recurrent ependymoma must be determined in a prospective clinical trial.

AUTHOR CONTRIBUTIONS

Statistical analyses were conducted by Drs. T.F. Cloughesy and A.B. Lassman.

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DISCLOSURE

Dr. Green reports no disclosures. Dr. Cloughesy served on a scientific advisory board for Genentech, Inc.; has received speaker honoraria from Excelixis Inc.; serves as a consultant to Adnexus™; serves on a speakers' bureau for Schering-Plough Corp.; receives research support from Genentech, Inc., Excelixis Inc., the IVY Foundation, and the Brain Tumor Funder's Collaborative; and has given expert testimony on behalf of Genentech, Inc., to the Oncology Drugs Advisory Committee. Dr. Stupp serves/has served on scientific advisory boards for and received honoraria from Roche, Schering-Plough Corp., Merck Serono, and Bristol-Myers Squibb; and serves on the editorial boards of *The Lancet Oncology*, *Neuro-Oncology,* and the *Journal of Clinical Oncology*. Dr. DeAngelis served on a scientific advisory board for Genentech, Inc.; serves on the editorial board of *Neurology*®; receives royalties from publishing *The Neurologic Complications of Cancer* (Oxford University Press, 2008); and has received research support from the NIH [UO1 CA-105663-01 (Participating Member in the NABTC)]. Ms. Woyshner and Dr. Ney report no disclosures. Dr. Lassman served on scientific advisory boards and/or consulted for Schering-Plough Corp., Sigma-Tau Pharmaceuticals, Inc., Bristol-Myers Squibb, ImClone Systems, Genentech, Inc., Eisai Inc., Enzon Pharmaceuticals, Inc., the National Comprehensive Cancer Network, Cephalon, Inc., IDBM Consulting, Ltd., Leerink Swan, LLC, and Gerson Lehrman Group; serves on the editorial board of the *Journal of Neuro-Oncology;* receives honoraria from Physicians' Education Resource, the Robert Michael Educational Institute, and Medical Communications Media; serves on a speakers' bureau for Schering-Plough Corp.; and receives research support from Keryx Biopharmaceuticals (PI), Sigma-Tau Pharmaceuticals, Inc. (PI), the National Cancer Institute [Radiation Therapy Oncology Group (Investigator) and Cancer Therapy Evaluation Program (Investigator)], the National Brain Tumor Foundation, Voices Against Brain Cancer, and the Dana Foundation.

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